REMARKS

Applicants acknowledge receipt of an Office Action dated April 6, 2005. In this response Applicants have amended claim 1. In addition, Applicants have added claims 42-46. Support for these amendments may be found in the specification, *inter alia*, on pages 21-24 and in the examples. Following entry of these amendments, claims 1-46 are pending in the application.

Claims 14-16 and 23-40 have been withdrawn from consideration as being drawn to non-elected subject matter. Thus, claims 1-13, 17-22, 41 are currently pending and under consideration.

Reconsideration of the present application is respectfully requested in view of the foregoing amendments and the remarks which follow.

Statement of Substance of Interview

As an initial matter, Applicants wish to thank Examiner Schnizer for the courtesies Extended to Dr. Sethuraman and Mr. Strain during a personal interview conducted on August 30, 2005. During the interview, Examiner Schnizer, Dr. Sethuraman and Mr. Strain discussed the outstanding rejections and the documents upon which each rejection was based.

Rejections Under 35 U.S.C. § 112

On page 3 of the Office Action, the PTO has rejected claims 1-13, 17-22, and 41 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection for the reasons set forth below.

In this response, Applicants have amended claim 1 to recite, in step (a), "a biological activity." Applicants submit that this amendment provides clear antecedent basis for the subsequent recitations of "the biological activity" and, further, that it is clear that the subsequent recitations of "the biological activity" refer to the same biological activity referenced in step (a).

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection under §112, 2nd paragraph.

Rejections Under 35 U.S.C. §102

On page 4 of the Office Action, the PTO has rejected claims 1-3, 7, 9, 10, 17, 18, and 41 under 35 U.S.C. § 102(b) as allegedly being anticipated by Chinol et al. (hereinafter "Chinol") (British Journal of Cancer 78(2): 189-197, 1998). In addition, the PTO has rejected claims 1-3, 7, 9, 10, 17, 18, and 41 under 35 U.S.C. § 102(a) as allegedly being anticipated by Decker et al. (hereinafter "Decker") (International Journal of Cancer 87:382-390, 2000). Applicants respectfully traverse these rejections.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See generally MPEP §2131.

Here, Applicants submit that none of the cited references disclose "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent" as recited in claim 1. In this response, Applicants amended step (a) to recite "a biological activity". The subsequent references to "the biological activity" refer to the *same* biological activity referenced in step (a).

With particular regard to Chinol, Applicants note that, in contrast to the presently claimed invention, the authors of the Chinol reference used ELISA to determine the titer of antibodies produced against avidin or mPEG modified avidin and used that to determine that modification of avidin with an average of 7 mPEG reduced the immunogenicity of the protein. Despite an the availability of a biological assay namely binding to biotin they chose to use the ELISA to determine titer of antibody produced as a response to repeated injection to determine the extent of desired modification. Thus, in contrast to Chinol's use of ELISA, according to the presently claimed invention, the biological activity in circulation (as measured by binding to biotin) could be measured as a guide to determine the extent of modification desired to protect avidin from host mediated inactivation instead of using the titer of antibodies produced in animals as a response to variously modified avidin as a guide to determining the desired extent of modification.

With particular regard to Decker, Applicants note that Deckert also fails to disclose assaying a first or second modified therapeutic agent after the first or second modified therapeutic agent "has been *administered to a subject*." While, Deckert used a biological

activity, in this case, binding affinity of huA33 to A33 antigen on SW1222 to determine the extent of PEGylation or protein modification. Deckert chose the extent of modification that gave less than 50% loss of binding affinity and determined that 30:1 ratio for PEG 5 and 15:1 for PEG 12 and PEG 20 based on acceptable loss of activity and used these ratios for all subsequent experiments. Thus, the extent of PEGylation was determined solely on acceptable loss of biological activity *without the use of in vivo studies*.

Deckert et al used classical immunogenicity study, the authors immunized mice four times with unmodified or huA33 modified at a ratio of 30:1 or huA33 modified at a ratio of 15:1 with PEG20. Antibody titer against unmodified and modified huA33 was determined and they found that animals treated with modified huA33 produced less anti-huA33 antibodies compared to animals treated with unmodified huA33. Two points need to be stressed here. They used two different PEGs but went into *in vivo* animal experiment not for determining the extent of modification but to find if the modifications reduced immunogenicity.

Still further, Applicants note that Deckert measured immunogenicity by determining the titer of anti-huA33 antibodies in treated animals. Interestingly, even though the authors had a biological activity that could have been used to determine the serum concentration of huA33, they did not use that method to determine the titer of huA33 in the serum of treated animal after first and subsequent experiments.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections under §102.

Rejections Under §103

On page 5 of the Office Action, the PTO has rejected claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez et al. (hereinafter "Alvarez") (Med. Pediatr. Oncol. 34(3):200-205, 2000) in view of Graham et al. (hereinafter "Graham") (Bone Marrow Transplant (21(9):879-885, 1998), and Francis et al. (hereinafter "Francis") (Int. J. Hematol. 68(1):1-18, 1998).

In addition, on page 8 of the Office Action, the PTO has rejected claim 4 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham and Francis, as applied

to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41 and further in view of U.S. Patent 6,531,122 to Petersen et al. (hereinafter "Petersen").

Also, on page 9 of the Office Action, the PTO has rejected claims 8, 11, and 20-22 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13,17, and 41, and further in view of Roberts et al. (hereinafter "Roberts") (J. Gen. Virol. 72:299-305,1991).

Finally, on page 10 of the Office Action, the PTO has rejected claims 18 and 19 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41, and further in view of U.S. Patent 4,678,812 to Bollin et al. (hereinafter "Bollin").

Applicants respectfully traverse each of the rejections under §103 for the reasons set forth below.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* MPEP §2143.03. Here, none of the cited references, taken either individually or in combination, teach or suggest "comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent" as recited in claim 1. As discussed above, the references to biological activity in this step relate to *the same* biological activity.

Further, and with particular regard to Alvarez, Applicants note that the objective of Alvarez's study was not to determine the extent of modification of asparaginase using various extents of modification with PEG. Further, Alvarez did not assay the biological activity of the agent, in this case asparaginase activity or asparagine level, after the first and subsequent injections in an effort to understand host-mediated inactivation.

Graham adds nothing to resolve the Alvarez's deficiencies. Alvarez used asparaginase modified with one modifying agent with a predetermined extent of modification and method of modification and studies the toxixicity of the a particular treatment mode. Alvarez does not report *comparison* of biological activity of the agent after first and subsequent treatments nor is the paper concerned with determining whether the agent is adequately protected against host mediated inactivation.

Francis, Petersen, Roberts and Bolin add nothing to resolve the deficiencies of the combination of Alvarez and Graham.

If an independent claim is nonobvious under §103, then any claim depending therefrom is nonobvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See MPEP 2143.03. Thus, Applicants submit that claims 2-13, 17-22 and 41, which ultimately depend from claim 1, are also non-obvious.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections under §103.

Newly Added Claims

In this response, Applicants have added claims 42-46.

With respect to independent claims 42-43, Applicants submit that none of the cited references, taken either individually or in combination, teach or suggest "comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer."

With respect to independent claim 44-45, Applicants submit that none of the cited references, taken either individually or in combination, teach or suggest "(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent (g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f)."

Finally, with respect to claim 46, Applicants submit that none of the cited references, taken either individually or in combination, teach or suggest the features of claim 1, from which claim 46 depends, "wherein the step of selecting a biological activity comprises selecting a biological activity other than either antigenicity or immunogenicity."

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

Respectfully submitted,

Date 6 October 2005

By S. A. Bent

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5540
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicants
Registration No. 29,768

Paul D. Strain
Attorney for Applicants
Registration No. 47,369

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.